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Manifestations in Institutionalised Adults With Angelman Syndrome Due to Deletion

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Undiagnosed institutionalised patients were reviewed in an attempt to identify those with Angelman syndrome (AS). The aim was to test these patients for deletion of chromosome 15(q11-13) and to describe the adult phenotype. The selection criteria included severe intellectual disability, ataxic or hypermotoric limb movements, lack of speech, a "happy" demeanour, epilepsy, and facial appearance consistent with the diagnosis. Patients were examined, medical records perused, and patients' doctors contacted as required. Genetic tests performed included routine cytogenetics, DNA methylation analysis (with probe PW71B), and fluorescence in situ hybridisation (with probes D15S10, GABRβ3, or SNRPN).

A deletion in the AS region was detected in 11 patients (9 males and 2 females) of 22 tested. The mean age at last review (March 1996) was 31.5 years (range 24 to 36 years). Clinical assessment documented findings of large mouth and jaw with deep set eyes, and microcephaly in nine patients (two having a large head size for height). No patient was hypopigmented; 1/11 patients was fair. Outbursts of laughter occurred in all patients but infrequently in 7/11 (64%) and a constant happy demeanour was present in 5/11 (46%). All had epilepsy, with improvement in 5/11 (46%), no change in 4 (36%), and deterioration in 2 (18%). The EEG was abnormal in 10/10 patients. Ocular abnormalities were reported in 3/8 patients (37.5%) and 4/11 (36%) had developed kyphosis. Two had never walked. All nine who walked were ataxic with an awkward, clumsy, heavy, and/or lilting gait. No patient had a single word of speech but one patient could use sign language for two needs (food and drink).

Our data support the concept that AS resulting from deletion is a severe neurological syndrome in adulthood. The diagnosis in adults may not be straightforward as some manifestations change with age. Kyphosis and keratoconus are two problems of older patients. Am. J. Med. Genet. 70:415–420, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: deletion chromosome 15(q11-13); epilepsy; intellectual disability

INTRODUCTION

Angelman syndrome (AS) is a severe genetic neurodevelopmental disorder, first described in three children at ages 5, 7, and 10 years [Angelman, 1965]. Many subsequent reports largely comprise descriptions of children [Clayton-Smith and Pembrey, 1992] of importance for early diagnosis [Fryburg et al., 1991]. The phenotype consists of flat occiput, posterior occipital groove, small widely spaced teeth, deep set eyes, midface hypoplasia, large mouth, and prognathism together with a happy disposition with frequent outbursts of inappropriate laughter [Williams et al., 1989; Clayton-Smith and Pembrey, 1992; Williams et al., 1995]. Other signs are ataxia, flapping of the hands when walking, absent speech, microcephaly, severe development disability, and an abnormal EEG pattern [Boyd et al., 1988]. The facial appearance of AS is characteristic after infancy but may be more subtle in older patients [Buntinx et al., 1995]. Heterogeneity was evident early with difficulty in providing a firm diagnosis in some cases [Kaplan et al., 1987]. The adult phenotype is not well known.

We report here the manifestations of 11 adults with AS shown to be due to DNA deletion. These cases were detected following testing of 22 undiagnosed institutionalised patients, all severely retarded. The data will be valuable in defining and delineating the adult phenotype and learning of the natural history of AS result-

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ing from deletion. No case of AS due to uniparental disomy (UPD) was detected.

METHODS

Patients

Patients resided in two institutions in New South Wales. The minimal criteria for diagnostic testing were severe intellectual disability, ataxic or hypermotoric movements, lack of speech, generally happy demeanour, epilepsy and large mouth and chin; namely AS was both possible and likely. At the institutions concerned most patients are severely retarded, and over 80% have epilepsy, with no speech and some difficulty walking. Thus, a happy disposition and consistent facial appearance were important inclusion criteria. The 2 institutions have between them approximately 900 patients. These patients were not systematically screened. Rather, ward sisters, doctors and allied health workers volunteered patients "likely" to have Angelman syndrome. These patients were then seen by AS together with at least one other clinician (TS, HB, HW). Assessment included history, physical examination and review of records. The patients' doctors and families were contacted for additional information where required. All patients had been institutionalised for at least 10 years, some since childhood. Of the initial 22 patients who were tested genetically, 11 had a deletion. There were 9 males and 2 females, mean age at last review (March 1996) was 31.5 years, range 24–36 years. Patient details are set out in Table I and patients 3, 32, 34–37, 40 are shown in Figures 1–7.

Genetic Testing

Peripheral blood was collected from each patient. Standard cytogenetic harvest followed 72 hour stimulated cultures and slides were prepared for GTG banding and FISH. DNA was extracted by standard techniques from the remainder of the specimen and this was used for methylation analysis. All patients had a normal banded karyotype at the 550 band stage of resolution. The probes used for FISH included D15S10, SNRPN, and GABRβ3 (Oncor, Gaithesburg) [Smith et al., 1995]. FISH detected the deletion in cases 32–41. In patient 3, a maternal deletion was established by the study of DNA polymorphisms [Smith et al., 1996]. Methylation analysis, performed in six patients (33–37, and 41), followed standard procedures [Dittrich et al., 1992] with enzymes HindIII/HpaII and probe PW71B (D15S63). All six patients showed the characteristic AS pattern (not shown). The order of testing depended

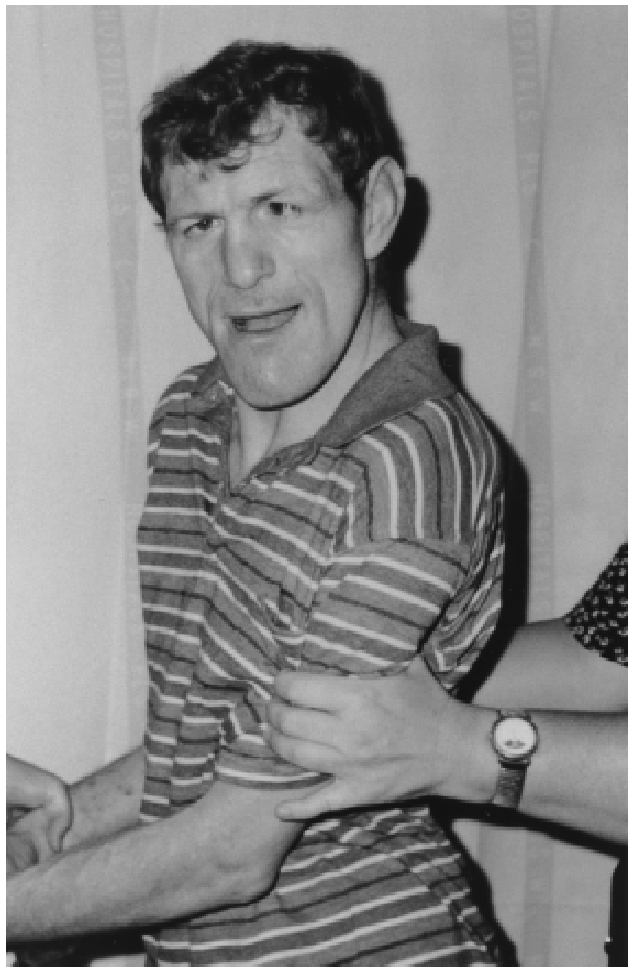

Fig. 1. Patient 3.

TABLE I. Patient Data*

ID	S/A	OFC centile	Ht centile	EI	EEG	HP	FY	Sl	Am	Ag	AOR	OA	SL	K	H	FL
3	M/35	<2	<3	yes	abn	no	yes	dis	yes	yes	yes	yes	no	yes	no	no
32	F/28	<2	3	no	abn	no	yes	sat	yes	no	yes	no	no	no	yes	no
33	M/33	50	<3	yes	abn	no	NK	sat	yes	no	yes	no	no	no	no	no
34	M/33	<2	3	yes	abn	F	yes	sat	yes	no	yes	NK	no	yes	no	no
35	M/36	3	<3	w	abn	no	yes	dis	no	no	no	no	no	yes	no	no
36	M/24	<2	NK	w	abn	no	NK	sat	no	yes	no	yes	2	no	yes	yes
37	M/33	<2	<3	no	abn	no	yes	dis+	yes	no	yes	no	no	yes	yes	yes
38	M/30	10	<3	yes	ND	no	NK	sat	yes	no	yes	no	no	no	no	no
39	F/31	2	25	yes	abn	no	yes	dis	yes	no	yes	NK	no	no	yes	yes
40	M/27	2	<3	no	abn	no	yes	dis	yes	yes	yes	NK	no	no	no	no
41	M/32	<2	<3	no	abn	no	no	dis	yes	no	yes	NK	no	no	yes	yes

*ID, patient identifying number; S, sex; A, age (in years); OFC, head circumference; Ht, height; EI, epilepsy improved; HP, hypopigmented; F, fair compared to family; FY, fair when young; SI, sleep; dis, disrupted; sat, satisfactory; Am, ambulant; Ag, aggressive episodes noted; AOR, abnormality of the occipital region, including flat occiput, occipital groove or occipital protuberance; OA, ocular abnormality; SL, sign language (Makaton); K, kyphosis; ND, not done; NK, not known; H, constant happy demeanour; FL, frequent outbursts of laughter.

Fig. 2. Patient 32.

mainly on the laboratory workload at the time of collection, but all patients had FISH analysis as a characteristic AS methylation result, while diagnosing the syndrome did not reveal the mechanism [Dittrich et al., 1992].

RESULTS AND DISCUSSION

We have described the findings of 11 adults with AS and a DNA deletion of chromosome 15. Several reports describe adult patients [Smith et al., 1989; Magenis et al., 1990; Williams et al., 1989; Reish and King, 1995] with the oldest being a male, age 76 years [Bjerre et al., 1984]. A review of 6 patients over 20 years old [Penner et al., 1993] and a review of 18 cases older than 16 years [Buntinx et al., 1995] provide information on aspects of the adult phenotype. Only two of the patients described have had a proven DNA deletion [Jauch et al., 1993; Reish and King, 1995] and none of the other cases reported contained information on DNA studies.

Anthropometrics

In our patients, 2/11 were non-ambulant and had never walked unassisted (Fig. 4, 5). None of the other patients showed loss of mobility. The head circumference (OFC) was on the 50th centile in one (patient 33), small in one (patient 38) and microcephalic in all the other patients. The height in 9/10 patients was on or below the 3rd centile. In patients 33 and 38 there were discrepancies between stature and OFC. No cerebral scans have been performed. The findings on height and OFC are similar to those for the younger deletional patients [Saitoh et al., 1994; Smith et al., 1996]. An abnormal occipital region (flat occiput, occipital groove and/or occipital protuberance) was common, present in 9/11 patients (82%) and this is at the upper end of the consensus criteria for AS (20–80%) [Williams et al., 1995].

Neurobehavioural Aspects

While all patients were generally of happy disposition, a constantly happy demeanour was present in 5/11 (46%) patients and outbursts of laughter occurred infrequently in 7/11 (64%). Three patients had aggressive episodes. Happy disposition was present in all and frequent laughter in most younger patients [Smith et al., 1996]. In 6/11 patients (54%) sleep was disrupted with periods of wakefulness and activity most nights and in patients 3 and 37 this occurred every night. Sleep problems were encountered in 86% of younger

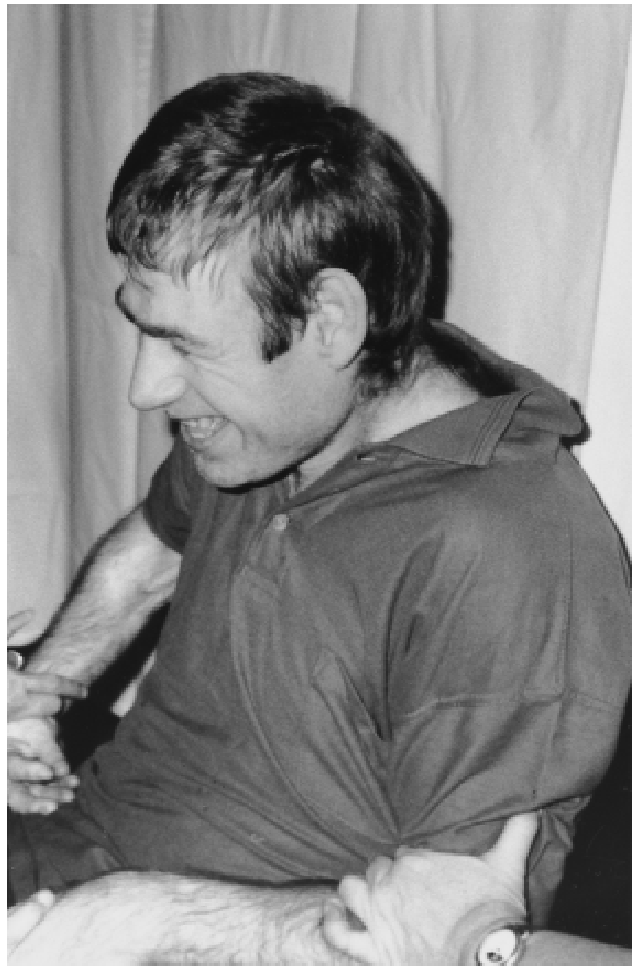

Fig. 3. Patient 34.

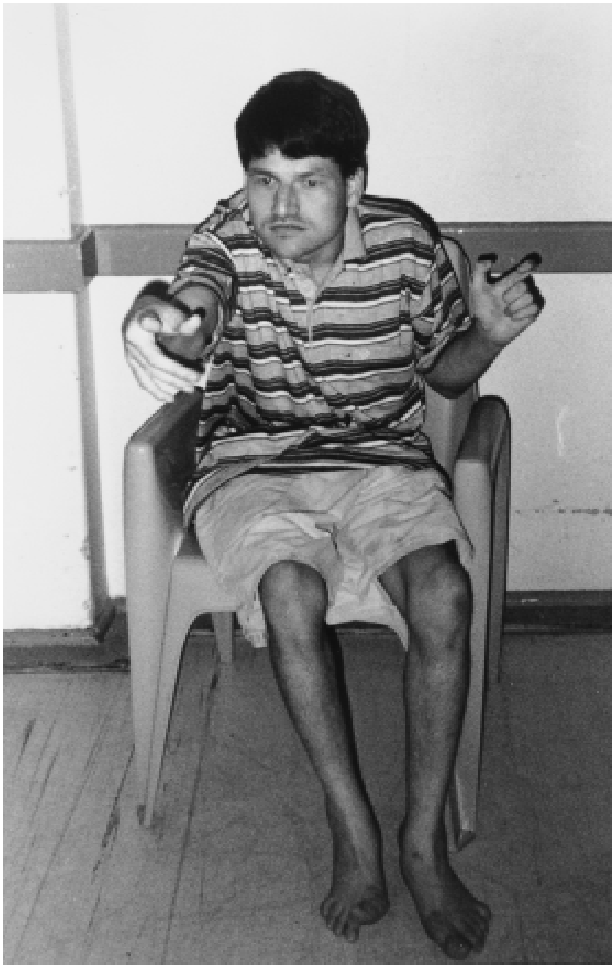

Fig. 4. Patient 35.

patients with DNA deletion [Smith et al., 1996] so that it seems that the sleep pattern overall shows improvement with age. Thus, our data support the findings that AS patients are less happy and "tend to calm down" as they grow older [Buntinx et al., 1995].

Epilepsy is a major component of AS with known variability of seizure type and frequency [Sugimoto et al., 1992]. In the 11 patients described here, the seizures included grand mal seizures, petit mal, and drop attacks. Some were isolated events and others episodic over a period of time. The epilepsy showed improvement in 5/11 (46%) of patients, as manifested by the "fit chart" records. In four patients the epilepsy showed no change with age and in two it was more difficult to control. These two patients required multiple medication. Improvement of epilepsy with age was shown in 7/7 epileptic AS patients after puberty [Matsumoto et al., 1992]. The AS patients in that study all had a deletion based on cytogenetics alone. More studies with long-term follow-up are needed to establish if there is an improvement in epilepsy with age in patients with AS, if the improvement is maintained and whether this is dependent on genetic classification.

The characteristic EEG changes can help confirm a diagnosis [Boyd et al., 1988], although other conditions may show a similar pattern, such as the Lennox Gastault epilepsy "syndrome" [Eslava-Cobos et al., 1989]. In analysing our data, interpretation of the EEG results was difficult as the assessments were undertaken by different neurologists who varied in their reporting. However, "slow spike and wave forms" were a frequent finding. EEG abnormalities have been reported to improve with age, showing diminution of seizure discharges after puberty [Matsumoto et al., 1992; Clayton-Smith, 1993]. Whenever it had been performed, the EEG was abnormal in the published reports of older patients [Buntinx et al., 1995; Bjerre, 1984; Williams et al., 1989]. All of our patients had an abnormal EEG. Thus, we could not provide confirmatory data to support an improvement in the EEG with age.

Our patients showed poor communication, with no speech and only one patient (patient 36) was able to perform any Makaton signs at all. A study of 11 children with AS showed that these children have poor communication development and difficulty in using gestural or sign language [Jolleff and Ryan, 1993]. In another study, factors affecting communication were investigated in six AS patients aged 20–40 years [Penner et al., 1993]. These individuals had oral motor dyspraxia and poor attention as well as intellectual handi-

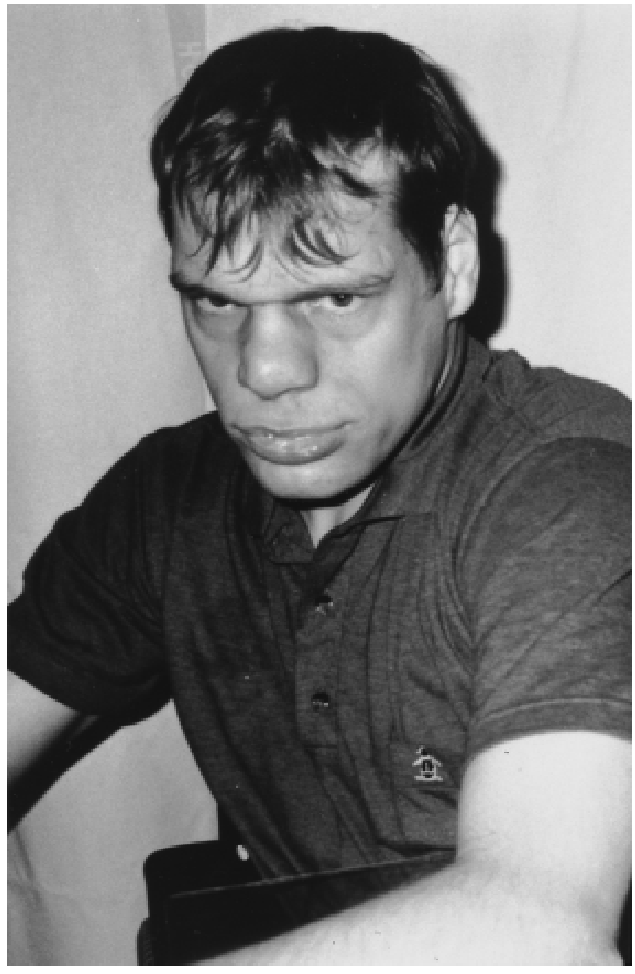

Fig. 5. Patient 36. He has had a broken nose on several occasions due to many falls and is now in a wheelchair usually wearing a helmet.

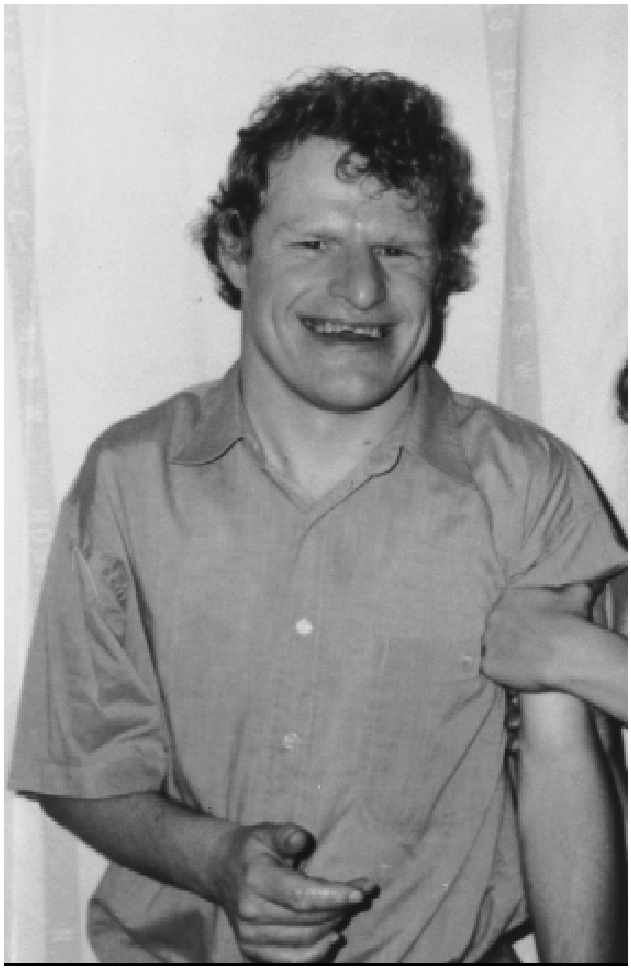

Fig. 6. Patient 37.

cap. No genetic data were given in these cases. In addition we found the level of functioning was low in our patients with all dependent for activities of daily living, a more severe level of functioning than suggested by the survey of 82 patients in the United Kingdom [Clayton Smith, 1993]. It is possible that in patients with deletional AS the severe affect becomes more pronounced with age but in our cohort, the poor functional level attained may also be due to the long institutionalisation. Of note here is a patient with DNA deletion who lived at home and had an IQ <20 at 50 years of age [Reish and King, 1995].

General Health

Overall the patients were healthy. Kyphosis had developed in 4/11 (36%). Abnormal ocular findings were present in 3/8 patients (37.5%) examined by an ophthalmologist. This included nystagmus and esotropia, while keratoconus was present in 2/8 patients (25%). The 76-year-old man [Bjerre, 1984] had advanced keratoconus at age 46 and after repeated intraocular hemorrhages was blind at 74 years. Ocular findings were not mentioned in the other reports of older cases. One study of eight children with AS, aged 3–10 years showed that 50% had ocular hypopigmentation but no other specific ocular abnormalities were noted [Dickinson et al., 1989]. On the limited data available, it appears that ocular problems develop with age in AS.

The life span of patients with AS is not known: the oldest reported case is 76 years [Bjerre, 1984] and the general health of patients is considered to be good [Buntinx et al., 1995; Clayton-Smith, 1993]. We could find reports of autopsies in only two patients. One died at age 24 of inhalation pneumonia following a seizure [Smith et al., 1989] and the other died of pneumonia at age 21 years [Jay et al., 1991]. Both patients were institutionalised from childhood. The former patient was deleted on DNA, hypopigmented, had severe epilepsy, and abnormal EEG, and the only abnormality at autopsy was horseshoe kidneys [Smith et al., 1989]. The latter patient was cytogenetically normal, had severe epilepsy and an abnormal EEG, and autopsy showed a small brain with nonspecific changes [Jay et al., 1991]. With no particular medical reason for a decreased life span, it appears that a significant number of adults remain undiagnosed. A study of adults in residential care may find other AS patients.

Pigmentation

Hypopigmentation is common in AS, reported in 73% of the younger group of patients with DNA deletion [Smith et al., 1996]. This is because a pigment gene at the distal end of the chromosome 15(q11-13) region is also deleted in many cases [Nichols, 1993]. Our data

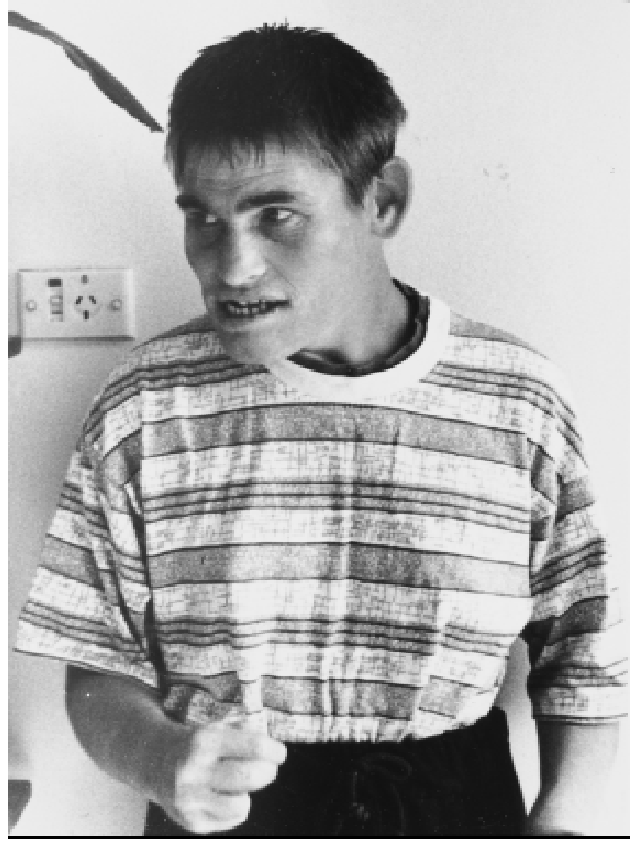

Fig. 7. Patient 40.

showed that no adult patient was hypopigmented, only one patient was fair (patient 34) and two patients had black hair (patients 38, 41). We could establish that 7/8 patients were "fair" when young. Thus, it appears from our cohort that the pigmentation process is ongoing and continues into adulthood. This was not the finding in the two other reported cases with deletion who were still fair at 33 [Magenis et al., 1990] and 50 years of age [Reish and King, 1995].

Frequency of AS in Institutions

Our finding of deletion in 11 patients of the 22 tested cannot be used as an estimate of the frequency of AS among institutionalised patients. Rather, our data acts as a pilot study alerting clinicians that in institutions there are undiagnosed patients with AS and that the phenotype is not as distinctive as in children. The patients described here all have a DNA deletion and it is not known if in adults, patients with UPD have different manifestations. We now aim to extend the review of patients and include others who were initially rejected as possible, but "less likely" to have AS. This may further assist in the recognition of cases and providing frequency data on institutionalised patients.

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